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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/776,910	02/06/2001	Robyn Joyce Russell	50179-087	3696

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Washington, DC 20005-3096

EXAMINER

RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/776,910

Applicant(s)

RUSSELL ET AL.

Examiner

Manjunath N. Rao, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 August 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 9-11 and 14-29 is/are pending in the application.
- 4a) Of the above claim(s) 18-29 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 18 is/are allowed.
- 6) ☒ Claim(s) 9-11 and 14-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☒ Certified copies of the priority documents have been received in Application No. 09068960.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8-4-04 has been entered.

Claims 9-11, 14-29 are currently pending and are present for examination. Claims 9-11, 14-18 are now under consideration. Claims 19-29 remain withdrawn from consideration as being drawn to non-elected invention.

Applicants' amendments and arguments filed on 8-4-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn the previous rejection held under 35 U.S.C. 102(b) in view of detailed argument provided by the applicants (see after-final amendment) to show that the claimed polypeptide does not read on the polypeptide disclosed in the reference.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 9, 14-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an enzyme with SEQ ID NO:8 and encoded by either SEQ ID NO:1, 3, or 5 and having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly and capable of hydrolyzing organophosphates, does not reasonably provide enablement for any such enzyme having at least 75% homology to SEQ ID NO:8 and differing from SEQ ID NO:8 in having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 9, 14-17 are so broad as to encompass any organophosphate degrading enzyme having at least 75% amino acid sequence identity to SEQ ID NO:8 and differing from SEQ ID NO:8 in having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of said enzymes broadly encompassed by the claims. Since the amino acid sequence of

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a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one said enzyme comprising the specific amino acid changes mentioned above. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The specification is limited to teaching the making and using amino acid sequence with SEQ ID NO:8 and differing from SEQ ID NO:8 in having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly and wherein said polypeptide continues to have organophosphate hydrolyzing activity but provides no guidance with regard to the making of variants and mutants as claimed or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims,

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the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any organophosphate hydrolyzing enzyme encoded by polynucleotides SEQ ID NOS:1, 3, or 5 having an amino acid sequence identity to SEQ ID NO:8 and differing from SEQ ID NO:8 in having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly, because the specification does not establish: (A) regions of the protein structure (except for the amino acid position 251) which may be modified without effecting activity; (B) the general tolerance of above enzymes to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including enzymes having 75% amino acid sequence identity to SEQ ID NO:8 and differing from SEQ ID NO:8 in having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly with an enormous number of amino acid modifications. The scope of the claims must bear a

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reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of enzymes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

In response to the previous Office action applicants argue that claims are directed to recombinant enzymes that have been engineered to have an amino acid sequence that retains the conserved amino acids of SEQ ID NO:8 and which has a specified amino acid at position 251 and that conserved/non-conserved sequences of SEQ ID NO:8 have been explained in the specification. Applicants also argue that the specification discloses amino acids that are necessary for the malathion resistance using which one of skill in the art can obtain the claimed recombinant carboxylesterase enzyme. Examiner respectfully disagrees that such arguments are persuasive to overcome the previously held and now maintained rejection. Examiner continues to maintain that claims 9, 14-17 while being enabling for an enzyme with SEQ ID NO:8, 10 or 13 and encoded by either SEQ ID NO:1, 3, 5, 7 and having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly and capable of hydrolyzing organophosphates, does not reasonably provide enablement for any such enzyme encoded by a polynucleotide that is either 80% or 95% homologous to SEQ ID NO:7 or any such enzyme having at least 75% homology to SEQ ID NO:8 and differing from SEQ ID NO:8 in having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

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make the invention commensurate in scope with these claims. Examiner disagrees with the applicants that providing information above conserved amino acids is sufficient for those skilled in the art to make variants. This is because while information regarding conserved amino acids is important and helpful, those skilled in the art need specific guidance regarding modifying specific amino acids that are not in the conserved region. While those skilled in the art know that conserved amino acids must not be modified in order to maintain the activity of the polypeptide, at the same time, need specific guidance regarding those amino acids that can indeed be modified without affecting the activity of the polypeptide. Such specific information is lacking in the specification. Without such guidance one of ordinary skill in the art would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein (i.e. structure of SEQ ID NO:8) and polynucleotides (SEQ ID NO:7) which may be modified without effecting activity; (B) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (C) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Hence the above rejection is maintained.

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Conclusion

Claim 18 is allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306/9307 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao, Ph.D.
Primary Examiner
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October 13, 2004